REMARKS

Claims 49-65 are currently pending in the application. Claims 66-81 have been cancelled. Claims 49-65 are currently amended. Support for these amendments can be found throughout the specification and is detailed below. Applicant acknowledges the renumbering of the claims under Rule 1.126.

Interview

Applicants appreciate the helpful suggestions regarding claim construction by Examiners Seharaseyon and Spector during a telephone interview on December 18, 2003. Applicants have incorporated the suggestions of the Examiners in order to more clearly define the invention.

Specifically, newly amended independent claim 51, which was previously dependent on claim 50, is drawn to a method for identifying a compound which specifically binds to the CCR5 chemokine receptor whose amino acid sequence is SEQ ID NO:5.

Also, newly amended independent claim 57, which was previously dependent on claim 50, is drawn to a method for identifying a compound as an agonist of the CCR5 chemokine receptor whose amino acid sequence is SEQ ID NO:5.

Additionally, newly amended independent claim 58, which was previously dependent on claim 50, is drawn to a method for identifying a compound as an antagonist of the CCR5 chemokine receptor whose amino acid sequence is SEQ ID NO:5.

Newly amended claims 51, 57 and 58 have been further amended to recite individual method steps and resolution steps that correspond to their respective preambles.

Information Disclosure Statement

Applicants have submitted an IDS statement with the instant response, along with the appropriate fee. Listed on the 1449 form is Samson et al. Molecular Cloning and Functional Expression of a New Human CC-Chemokine Receptor Gene, Biochemistry 35:3362-3367, which published March 19, 1996, which is later than the 3-1-1996 filing date of Applicant's earliest priority document EP 96870021.1.

Also listed on the 1449 form of the IDS is WO 97/22698 entitled CHEMOKINE RECEPTORS 88-2B[CKR-3] AND 88C AND THEIR ANTIBODIES, filed December 20, 1995, published June 26, 1997, from which U.S. Patent No. 6,265,184 ('184) entitled "Polynucleotides Encoding Chemokine Receptor 88C" filed on December 20, 1995, and issued on July 24, 2001, U.S. Patent No. 6,268,477 ('477) entitled "Chemokine Receptor 88-C" filed on June 7, 1996, and issued on July 31, 2001, claim priority. Applicants note that '184 and '477 were considered by the Examiner in an IDS filed 5-10-02.

DECLARATIONS UNDER 37 C.F.R. § 1.131

Declarations by Pierre Nokin, Marc Parmentier, Alfred Gray , Eric Van Malderen, Michel Samson, Gilbert Vassart, and Frederic Libert under 37 C.F.R. § 1.131 have been submitted with the instant response, for the purpose of establishing that the instant invention was conceived prior to December 20, 1995 (the earliest effective filing date of the '184 and '477 patents, and of WO 97/22698) and that the invention was reduced to practice with due diligence shortly thereafter. The submission of the above-identified Declarations Under 37 C.F.R. § 1.131 suffice to establish that U.S. Patent Nos. 6,265,184 and 6,268,477 and WO 97/22698 are not prior art to Applicants' claimed invention. Applicants' invention claimed in the instant pending claims was conceived and reduced to practice in the United States prior to the earliest effective filing date (December 20, 1995) of U.S. Patent Nos. 6,265,184 and 6,268,477 and WO 97/22698.

Prior to the earliest effective filing date (December 20, 1995) of U.S. Patent Nos. 6,265,184 and 6,268,477, and WO 97/22698, Applicants' claimed invention was conceived and reduced to practice as evidenced by the following facts:

- On December 12, 1995, a manuscript entitled "Molecular Cloning And Functional Expression Of A New Human CC-Chemokine Receptor Gene" (hereinafter referred to as "the CCR5 Manuscript") was sent by inventor and lead author Marc Parmentier for submission for publication in the United States scientific journal *Biochemistry*. The CCR5 manuscript described the sequence of the human CCR5 receptor, the expression in a stable recombinant cell line of the human CCR5 receptor, and the pharmacology (ability to recognize a set of specific chemokines in vitro) of the human CCR5 receptor. The CCR5 manuscript was the basis for U.S. patent application Serial No. 09/939,226 (the above-identified application). The CCR5 manuscript was sent to the United States on December 12,

1995, addressed to Dr. Gordon G. Hammes, Editor of *Biochemistry*, Room 081 Yellow Zone, Duke South, Duke University Medical Center, Durham, North Carolina 27710, U.S.A. (See Declaration Of Pierre Nokin, ; Declaration Of Marc Parmentier, Exhibit G).

- From December 12-14, 1995, the CCR5 Manuscript was in route via mail services from Marc Parmentier to Dr. Gordon G. Hammes, Editor of *Biochemistry*, in Durham, North Carolina U.S.A. (See Declaration Of Marc Parmentier,).
- On December 14, 1995, the CCR5 Manuscript was received by *Biochemistry*. Evidence of receipt of the CCR5 Manuscript by *Biochemistry* in the United States is shown on the top of the first page of the CCR5 Manuscript as published in *Biochemistry* on March 19, 1996 that states, "Received December 14, 1995." (See Declaration Of Marc Parmentier, Exhibit H). Additionally, a letter from Mary E. Scanlan, the Director of the Publications Division of the American Chemical Society (the publisher of *Biochemistry*) confirms that *Biochemistry* received the CCR5 Manuscript on December 14, 1995. (See Exhibit A attached hereto; Declaration Of Alfred Gray,).
- From December 14, 1995 through January 4, 1996, *Biochemistry* followed its standard operating procedures designed to ensure that submitted articles are diligently reviewed for publication. Under *Biochemistry's* standard operating procedures, within 1-3 days after receipt (December 14-17, 1995), the CCR5 Manuscript would have been assigned to an associate with appropriate training and expertise for the type of research represented by the CCR5 Manuscript. In the December 14-17, 1995 time period, the CCR5 Manuscript was assigned to Associate Editor Dr. Earl Davie for review. (See Declaration Of Alfred Gray,). The Associate Editor then reviews the article and considers a choice of independent reviewers to which to send the article for review. The CCR5 Manuscript was sent out by *Biochemistry* for review by independent reviewers on January 4, 1996. (See Declaration Of Alfred Gray,). Following the above procedures, the CCR5 Manuscript was subsequently accepted for publication, and published on March 19, 1996. (See Exhibit A attached hereto; Declaration Of Marc Parmentier, Exhibit H).
- Sometime after December 12, 1995, Marc Parmentier received a confirmation receipt from *Biochemistry*. The confirmation receipt lists that the CCR5 Manuscript was "Rec'd: DEC 14, 1995" confirming that *Biochemistry* received the CCR5 Manuscript on December 14, 1995. The confirmation receipt also states, "The foregoing manuscript has been assigned to

the Associate Editor . . . ." The confirmation receipt from *Biochemistry* is undated, but it was received shortly after the December 12, 1995 submission to *Biochemistry*. (See Declaration Of Marc Parmentier, Exhibit I).

- Between the submission of the CCR5 Manuscript to the United States scientific journal *Biochemistry* on December 12, 1995 and December 19, 1995, Pierre Nokin, the CEO of Euroscreen (the assignee of Serial No. 09/939,226), had at least one conversation with the inventors of Serial No. 09/939,226 regarding sending the CCR5 manuscript to a patent attorney for preparation and filing of a patent application based on the CCR5 manuscript. (See Declaration Of Pierre Nokin,).
- On December 20, 1995, Pierre Nokin, the CEO of Euroscreen, had a telephone conversation with patent attorney Eric Van Malderen relating to instructions for preparation of a patent application on the discovery of CCR5. During the conversation, patent protection strategies inside and outside of the United States were discussed, and the filing of a European Patent Application followed by the filing of a PCT international application at the convention date was determined to be a prudent course of action for United States patent protection. (See Declaration Of Pierre Nokin; Declaration Of Eric Van Malderen).
- On December 21, 1995, Pierre Nokin sent a copy of the CCR5 manuscript submitted to the United States scientific journal *Biochemistry* to patent attorney Van Malderen for preparation of a patent application based on the CCR5 manuscript. (See Declaration Of Pierre Nokin, Exhibit D; Declaration Of Eric Van Malderen).
- From December 21-27, 1995, a copy of the CCR5 manuscript was in route via mail services from Pierre Nokin to patent attorney Van Malderen. This time interval includes the Christmas holiday on Monday, December 25, 1995.
- On December 27, 1995, patent attorney Van Malderen received Dr. Pierre Nokin's letter dated December 21, 1995 (based on the "Received 27-12-1995 Office Van Malderen" date stamp) which enclosed a copy of the CCR5 manuscript. (See Declaration Of Eric Van Malderen, Exhibit K).
- During December 27, 1995 through March 1, 1996, patent attorney Van Malderen diligently prepared a patent application entitled "CC-Chemokines Receptor And Nucleic Acid Molecule Encoding Said Receptor" that was filed in the European Patent Office on March 1, 1996. (See Declaration Of Eric Van Malderen).

- In particular, during the time period from December 27, 1995 through January 5, 1996, patent attorney Van Malderen diligently prepared a first draft of the patent application entitled "CC-Chemokines Receptor And Nucleic Acid Molecule Encoding Said Receptor" (even though the New Year's holiday occurred during this time period). (See Declaration Of Eric Van Malderen).
- On January 5, 1996, patent attorney Van Malderen sent a preliminary draft of the patent application entitled "CC-Chemokines Receptor And Nucleic Acid Molecule Encoding Said Receptor" to the attention of Dr. Pierre Nokin at Euroscreen for review by Dr. Pierre Nokin and the inventors. (See Declaration Of Eric Van Malderen, Exhibit L; Declaration Of Pierre Nokin).
- On January 31, 1996, patent attorney Van Malderen sent a letter to Dr. Pierre Nokin at Euroscreen requesting that Dr. Nokin obtain additional information from the inventors for the patent application. (See Declaration Of Eric Van Malderen, Exhibit M; Declaration Of Pierre Nokin).
- On February 15, 1996, Dr. Pierre Nokin sent a letter to patent attorney Van Malderen attaching a revised version of the patent application containing revisions by the inventors. (See Declaration Of Pierre Nokin, Exhibit E).
- On February 19, 1996, patent attorney Van Malderen received Dr. Pierre Nokin's letter dated February 15, 1996 (based on "Received 19-2-1996 Office Van Malderen" date stamp). (See Declaration Of Eric Van Malderen, Exhibit N).
- On February 21, 1996, patent attorney Van Malderen sent a copy of the revised patent application to Inventor Marc Parmentier for Marc Parmentier's review. (See Declaration Of Eric Van Malderen, Exhibit 0).
- Prior to or on February 29, 1996, patent attorney Van Malderen had a conversation with Dr. Pierre Nokin in which Dr. Nokin advised patent attorney Van Malderen to file the patent application entitled "CC-Chemokines Receptor And Nucleic Acid Molecule Encoding Said Receptor" with the European Patent Office. Dr. Pierre Nokin also sent patent attorney Van Malderen a letter dated February 29, 1996 requesting that patent attorney Van Malderen file the revised and completed version of the patent application entitled "CC-Chemokines Receptor And Nucleic Acid Molecule Encoding Said Receptor" with the European Patent Office. (See Declaration Of Eric Van Malderen, Declaration Of Pierre Nokin, Exhibit F).

- On March 1, 1996, patent attorney Van Malderen filed the patent application entitled "CC-Chemokines Receptor And Nucleic Acid Molecule Encoding Said Receptor" with the European Patent Office. This application was given a filing date of March 1, 1996 and assigned Application No. EP 96870021.1. (See Declaration Of Eric Van Malderen).
- From the time patent attorney Van Malderen initially learned about the CCR5 discovery on December 20, 1995, until filing the patent application entitled "CC-Chemokines Receptor And Nucleic Acid Molecule Encoding Said Receptor" on March 31, 1996, patent attorney Van Malderen had a full docket of other patent matters to work on, but patent attorney Van Malderen was diligent in his preparation of the patent application entitled "CC-Chemokines Receptor And Nucleic Acid Molecule Encoding Said Receptor" and handled applications in the chronological order in which they were submitted. (See Declaration Of Eric Van Malderen).
- From December 23, 1995 to January 2, 1996, the four listed inventors of U.S. patent application Serial No. 09/939,226 were on vacation for the Christmas and New Year's holidays. (See Declaration Of Marc Parmentier, Declaration Of Michel Samson, Declaration Of Gilbert Vassart, Declaration Of Frederic Libert,).
- Prior to December 20, 1995 (the earliest effective filing date of U.S. Patent Nos. 6,265,184 and 6,268,477), the inventors of Serial No. 09/939,226 had conceived of the invention as claimed in Serial No. 09/939,226. The invention was reduced to practice with due diligence shortly thereafter. (See Declaration Of Marc Parmentier, Declaration Of Michel Samson, paragraph 3; Declaration Of Gilbert Vassart, Declaration Of Frederic Libert,). Thus, U.S. Patent Nos. 6,265,184 and 6,268,477 are not prior art to Applicants' claimed invention.

Thus, Applicants' invention claimed in the pending claims was conceived and reduced to practice in the United States prior to the earliest effective filing date (December 20, 1995) of U.S. Patent Nos. 6,265,184 and 6,268,477 and WO 97/22698 .

Priority

The Office Action requires that the priority information be updated to indicate the allowed application, (Serial Number 08/833,752). Applicant has updated the priority information as required.

Claim Rejections – 35 USC 112, second paragraph,

Claims 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

A. The Office Action asserts that there is insufficient antecedent basis for the limitation "said candidate compound" recited in line 2 of Claim 49.

Applicant has amended said limitation in line 2 to recite "a candidate compound", thereby obviating the need for antecedent basis. Applicant respectfully requests reconsideration and withdrawal of the rejection.

B. The Office Action asserts that there is insufficient antecedent basis for the limitation "said portion thereof" recited in Claim 50.

Applicant has deleted the limitation "said portion thereof" from Claim 50. Applicant notes that the term "portion thereof" was not recited in the claims as originally filed, and that the term was introduced into Claim 50 by preliminary amendment. In a subsequent supplemental preliminary amendment, the term was deleted from the preamble of Claim 50, but was inadvertently not deleted from all of the method steps of claim 50. Applicant notes that the term clearly has no antecedent basis. Applicant has amended Claim 50 so that it no longer recites the term "portion thereof", and respectfully requests reconsideration and withdrawal of the rejection.

C. The Office Action asserts that Claims 50, 52, 66 and 68 are indefinite in their recitation of the term "a portion thereof" because the term "a portion thereof" is not defined in the specification.

Claims 50 and 52, as amended, do not contain the term "a portion thereof". Claims 66 and 68 have been canceled. Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejection.

D. The Office Action asserts that Claims 52 and 68 are indefinite in their recitation of the term "signaling activity of said CCR5" because "it is unclear what signaling activity is contemplated".

Solely for the purpose of more clearly defining Applicant's invention, Applicant has amended the term "signaling activity of said CCR5" recited in Claim 52 to "G- protein coupled signaling activity". Support for the amendment clarifying that the signaling activity is a G-protein coupled signaling activity, is found in the specification in the section entitled *Identification of an inactive CCR5 receptor.* In describing the truncated CCR5 receptor (SEQ ID NO:6), Page 30 discloses that "such a truncated protein is certainly not functional in terms of chemokine-induced signal transduction: it lacks the third intracellular loop and C-terminal cytoplasmic domains, the two regions involved primarily in G protein coupling". Claim 68 has been canceled.

In view of the amendment clarifying the nature of the signaling activity of CCR5, and the cancellation of Claim 68, Applicant respectfully requests reconsideration and withdrawal of the rejection.

E. The Office Action asserts that Claims 55 and 71 are indefinite in their recitation of the term "intracellular cascade" because "it is unclear what are the cascades present in a cell are monitored in the instant invention".

Solely for the purpose of more clearly defining Applicant's invention, Applicant has amended Claim 55 so that it no longer recites the term "intracellular cascade". Therefore, Applicant respectfully requests withdrawal of the rejection.

However, claim 53 has been amended so that it recites " wherein said detecting is performed by measuring the modifications of cell metabolism resulting from the stimulation of an intracellular cascade, instead of by monitoring the acidification rate of said host cell. In response to a similar potential rejection being applied to Claim 53, Applicant notes that the binding of a compound by the CCR5 receptor can be detected by measuring the modification of cell metabolism resulting from the stimulation of intracellular cascades upon receptor binding of the compound. The recitation of claim 53 indicates that the specific cascades which mediate the change in cell metabolism which is ultimately detected in the recited method, are secondary, and consequently need not be specifically defined. Support for the amendment is found in the specification which discloses measuring the resulting changes in cell metabolism with a microphysiometer.

Support for this amendment is found in the specification on Page 25, lines 4-9, which discloses:

"The microphysiometer allows the real time detection of receptor activation, by measuring the modifications of cell metabolism resulting from the stimulation of intracellular cascades [33]. Several studies have already demonstrated the potential of microphysiometry in the field of chemokine receptors. Modifications of metabolic activity in human monocytes, in response CC-chemokines, were monitored using this system [43]",

on Page 26, lines 12 to 15, which discloses:

"The concentrations necessary for obtaining a biological response as determined by using the microphysiometer are in the same range as those measured by intracellular calcium mobilisation for the CCR1 [31], the CCR2A and B [8], and the CCR3 [10] receptors",

and on Page 25, lines 13 to 17, which discloses:

"Ligands belonging to the CC- and CXC-chemokine classes were tested on the *CCR5* transfected CHO-K1 cells. Whereas MIP-1.alpha., MIP-1.beta. and RANTES were found to be potent activators of the new receptor (FIG. 4), the CC-chemokines MCP-1, MCP-2 and MCP-3, and the CXC-chemokines GRO.alpha. and IL-8 had no effect on the metabolic activity, even at the highest concentrations tested (30 Nm)".

In view of the clarification of the amendment to Claim 53, Applicant respectfully requests that a 112 second paragraph rejection will not be levied against claim 53.

Claim Rejections 35 U.S.C. 112, first paragraph,

Claims 50, 62, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the invention was filed, had possession of the claimed invention.

The Office Action states that "The specification discloses CCR5 and CCR5 deletion mutant of SEQ ID NO:5 and 6. This meets the written description and enablement provisions of 35 USC 112, first paragraph". However, the Office Action asserts that "the specification does not disclose all the various portions of the CCR5 receptors", and that claims 50, 62, 66 and 68

"as written, therefore, encompass polypeptide sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph".

While not necessarily acquiescing to the rejection, Applicant has deleted the term "a portion thereof" from Claims 50 and 52. Claims 66 and 68 have been cancelled. Reconsideration and withdrawal of the rejections is respectfully requested.

Claims 50, 62, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains , or with which it is most nearly connected, to make and/or use the invention.

The Office Action states that "Applicant describes the polypeptide sequences SEQ ID NO:5 and 6 yet contemplates various portions of CCR5". The Office Action further states that "The lack of description of the various portions CCR5 polypeptide in the specification does not enable one of skill in the art make or use the invention".

While not necessarily acquiescing to the rejection, Applicant has deleted the term "a portion thereof" from Claims 50 and 52. Claims 66 and 68 have been cancelled. Reconsideration and withdrawal of the rejections is respectfully requested.

CONCLUSION

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

Date: 3/2/04

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